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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,068	HEN ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67,68,70-72 and 89-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67,68,70-72 and 89-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 19 July 2005 have been entered. Claims 1 – 66, 69, and 73 – 88 have been cancelled. Claims 67, 68, 70 – 72, and 89 – 92 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Information Disclosure Statement

4. The information disclosure statement filed 6 May 2005 fails to comply with 37 CFR 1.97(c) because it lacks a statement as specified in 37 CFR 1.97(e) and the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

Withdrawn Rejections and Objections

5. The following rejections or objections made in the previous office action are withdrawn:

The rejection of claim 86 under 35 USC 112, 2nd paragraph. The claim is canceled.

The rejection of claims 67 – 68, 70 – 72 under 35 USC 102 as being anticipated by Yoshimura. Applicant's amendments require that certain agents be administered which are not taught by Yoshimura.

The rejection of claims 67 – 68, 70, and 71 under 35 USC 102 as being anticipated by Zhang. Applicant's amendments require that certain agents be administered which are not taught by Zhang.

The rejections of claims 67 – 68, 70, and 90 under 35 USC 102 as being anticipated by Wallace. Applicant's arguments are persuasive; Wallace does not fairly teach administration of an agent that increases the amount of cell-division marking compound incorporated into cells.

The rejections of claim 67 under 35 USC 103 as being obvious over Fujii in view of Yoshimura. Neither Fujii nor Yoshimura teach the agents recited in claim 67 as amended.

Rejections and Objections Necessitated by Amendment

Claim Objections

6. Claim 67 is objected to because of the following informalities: it appears to be missing the word "wherein" at the beginning of the final paragraph. Appropriate correction is required.

Priority Determination

7. 35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

8. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because support for claims 67 – 68 and 70 – 72 insofar as they are drawn to agents which upregulate the sonic hedgehog pathway, and claims 89 – 92 is provided in provisional application 60/526190 (filed 1 December 2003) but not in provisional application 60/442081 (filed 23 January 2003), the examiner has determined that the effective filing date for those claims is 1 December 2003. Applicant clearly had not conceived of the use of any agonists of the sonic hedgehog pathway in methods to detect brain progenitor cell division in application 60/442081. Applicant did not traverse this priority determination in the remarks filed 19 July 2005. Thus the effective filing date for all claims is 1 December 2003, as claim 67, from which all other claims depend, has been amended to recite "agents that upregulate the sonic hedgehog pathway".

Claim Rejections - 35 USC § 112

9. Claims 67 – 68, 70 – 72, and 89 – 92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The examiner cannot find support for the limitation "2 hours to 28 days" recited in claim 67, step (c) from the text cited by applicant on p. 5, first paragraph of the remarks. While support for the "28 days" limitation can be found at page 33 line 26, the examiner cannot find

support for the range. Page 33 lines 19 – 22 disclose administration of BrdU every 2 hours, but the limitation in claim 67 part (c) refers to the interval between BrdU administration and sacrifice; page 33 lines 19 – 22 disclose the first sacrifice was 24 hours after the final BrdU administration.

10. Claims 67 – 68 and 70 - 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 recites an improper Markush group. The claim recites "growth factor receptor activators or modulators". This phrase is indefinite because it is unclear whether the modulators are growth factor receptor modulators or if they are modulators in general. The artisan could not determine the metes and bounds of the claims.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 112

11. Claims 67 – 68, 70 – 72, and 89 – 92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of the agents listed in claim 67, part (a), to a non-human subject for several days to one month, administering an nucleotide analog such as BrdU or ^{3}H-thymidine, does not reasonably provide enablement for all methods of determining whether said agents increase brain progenitor cell division, or for administration of all compounds, unlimited by structure, which are markers of cell division. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for the reasons made of record on pp. 3 – 6 of the office action mailed 14 April 2005 and explained below.

On p. 7 of the remarks, applicant argues that because a reasonable number of agents which could be administered to the subject are enabled, then the claim should be considered enabled as a matter of law. Applicant's arguments have been considered and are persuasive; the examiner concedes that it would be possible to administer the agents recited in claim 67, part (a) in this method, as it is a screening method. The claim is considered enabled over the scope of agents recited in (a). Applicant cites *U.S. v. Telectronics*, *SRI Int'l v. Matsushita*, and *Hybritech Inc.* as being supportive of the argument that not all embodiments must be disclosed. The examiner agrees that these points are supportive of the argument. The claims are deemed

enabled over the full scope of agents recited in claim 67 part (a). However, claims stand rejected for the reasons explained below.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case, the nature of the invention, determining whether an agent increases brain progenitor cell division, is complex. The claims are broad in that they are drawn to administration of any compound which is a marker of cell division to the subject, with the exception of claims 70 and 72 which are limited to BrdU administration and detection respectively. Furthermore the claims are deemed to be broad because they are drawn to methods of determining whether "brain progenitor cell division" is increased by the agent.

On p. 8 of the remarks, applicant directs the examiner's attention to Figures 2C and 2D, as well as to p. 40 of the specification for support for the assertion that BrdU and either NeuN or GFAP co-label cells. The cited figures are very difficult to interpret. However, the examiner concedes that GFAP or NeuN can be used along with BrdU to determine which of the BrdU-positive cells are glia or neurons, respectively. This co-labeling would allow the artisan to conclude that the cells which have incorporated the marker of cell division are in fact glia or neurons, but such co-labeling is not required in any of the claims. Instant claim 67, from which all other pending claims depend, instructs the artisan to conclude that brain progenitor cell division is increased after observing that an increased amount of the compound (that is, the marker of cell division) is greater in the subject receiving the test agent than in the control. This conclusion is not warranted based on the data that would be provided by the recited steps of the method. Ettlin (1993. In Vivo 7(4):315-324) teaches that BrdU is indicative of increased proliferation, which can be due to either subtle cytotoxicity or to the presence of a tumor.

The guidance and working examples in the specification are not sufficient to allow a skilled artisan to conclude that any observed changes are actually in brain progenitor cells. The specification provides definitions for several terms (see pp. 17 – 21) but does not include a specific definition of the term "brain progenitor cell". The prior art teaching of Okano (2002.

Keio J Med 51:115-128, cited in previous office action) indicates that both neural and glial progenitor cells exist (see Figure 1, p. 116); the term "brain progenitor cell" necessarily includes both, and can is so broad that it reasonably includes any cell type that is a progenitor and is in the brain. For example, it includes those progenitors which give rise to blood vessels within the brain. The specification discloses methods of determining whether an agent increases the amount of BrdU taken up by a cell. However, Kee et al. (2002. J. Neurosci. Methods 115:97-105, cited in previous office action) teach that BrdU is taken up by dividing cells (p. 97, second column). The scope of dividing cells is considerably larger than progenitor cells, as progenitor cells by definition are those that give rise to additional cell types (i.e. as explained on p. 116 of Okano, neural progenitor cells give rise to multiple types of neurons, and glial progenitor cells give rise to astrocytes and oligodendrocytes), but there are of course cells that divide and are not progenitor cells, including tumors, for example. Methods that use BrdU are not specific for progenitor cells. Similarly, Ki-67 is expressed in all cells undergoing mitosis (Scholzen et al. 2000. J Cell Physiol 182:311-322, cited in previous office action; see p. 312, second column) and is not specific to progenitor cells. The claims do not require that the artisan determine whether the compound which is a marker of cell division is actually expressed in neurons or glia, for example, thus the artisan would not be able to conclude, based on the data that would be obtained in the claimed method, that the increases in the amount of the compound are indicative of changes in brain progenitor cell division, a compounds which are markers of cell division, are clearly taken up by cancer cells and unhealthy cells which are not brain progenitor cells.

Claim 67 recites "a compound which is a marker of cell division", however there is no structural limitation for the compound. The specification discloses methods based on the immunhistochemical recognition of BrdU, which is incorporated into the DNA of dividing cells, and the prior art clearly indicates that the Ki-67 protein is a marker of cell division (see, for example, Kee et al. 2002. J. Neurosci. Methods 115:97-105, cited in the previous office action). However with the exception of claims 70 and 72 there is no requirement that a BrdU-based detection method be used. Claim 72 recites staining the tissue sections with an anti-BrdU antibody, but it depends from claim 67 which does not require the administration of BrdU. Claim 67 is sufficiently broad that it encompasses any method of determining, but the specification only provides working examples wherein BrdU is used as the method of determining whether changes in cell division have occurred. Kee et al. teach that Ki-67 is a marker of cell division,

but this is produced intracellularly. In order for Ki-67 to work in the claimed method, it would have to cross the blood-brain barrier, be taken up by cells, and transported to the nucleus. This would not be expected to work, as the blood-brain barrier excludes about 98% of molecules, and proteins generally are not well-transported across the barrier (see Pardridge, 2002. Nature Reviews Drug Discovery 1:131 – 139). Furthermore Etlin teaches that measuring Ki-67 in animal tissues is not a reliable measure of cell proliferation (see p. 318, final sentence). While the specification is enabling for administering a radiolabeled nucleotide such as ^{3}H-thymidine or nucleotide analog such as BrdU as compounds which are markers of cell division, the specification is not enabling for administration of all compounds which are markers of cell division. Given the state of the prior art the artisan would not expect those markers which either are proteins, or are produced intracellularly, to be effective in the method of claims 67 – 68, 71 – 72, and 89 – 92.

12. Claims 67 - 68, 70 – 71, and 89 – 92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant argues, on p. 9 of the remarks, that the rejection should be withdrawn for the following reasons:

1) The amended claims are drawn to test agents, a reasonable number of which are described.

2) The specification provides representative examples of brain progenitor cells.

3) The amended claims recite specific time periods.

Applicant's arguments have been fully considered, and are persuasive in part. The examiner agrees that the amendments to the claims are such that the specification provides adequate written description for the test agents and for the specific time periods. However, the specification does not provide an adequate written description of "brain progenitor cells". While several terms are explicitly defined on pp. 17 – 21 of the specification, "brain progenitor cell" is not among these terms. Applicant has not adequately described a reasonable number of members of this broad genus. This is a broad genus that includes, at the minimum, neural and glial progenitor cells, and could reasonably include any progenitor cell (i.e. blood vessel progenitor cells) that are in the brain and tumor progenitors. Applicant directs the examiner's

attention to p. 40 lines 10-23 for support of the written description of brain progenitor cells. This section of the specification describes the result of experiments wherein BrdU-positive cells were also stained for the presence of either NeuN, a marker of neurons, or GFAP, a marker of glia. These are not brain progenitor cells, they are the progeny of neural stem cells (see Okano, p. 116, Figure 1). The specification does not provide a disclosure of the reasonable number of members of the genus "brain progenitor cells". Furthermore the specification has not described the entire genus of "determining" steps, although certain subgenera (i.e. *specific* instantiations of BrdU-based methods) have been described. Similarly, claim 67, part b, recites administering "a compound which is a marker of cell division", but the specification has not described a reasonable number of members of the genus of said compounds.

Claim Rejections - 35 USC § 102

13. Claims 67, 68, and 70 – 72, are rejected under 35 U.S.C. 102(b) as being anticipated by Malberg (cited in previous office action).

Malberg et al. teach a method of determining whether an agent increases brain progenitor cell division, wherein the agent is either fluoxetine or haloperidol (see p. 9104, last full paragraph). These fall within the categories of selective serotonin reuptake inhibitors and antipsychotic inhibitors, respectively, recited in claim 67. The agents were administered for 21 days (fluoxetine) or 1 – 28 days (haloperidol, see p. 9104, last full paragraph), BrdU was administered, (see paragraph spanning pp. 9104 – 9105), animals were sacrificed after 2 hrs – 28 days (see p. 9105, Figure 1, part A), cells labeled with BrdU were counted and compared to controls (see paragraph spanning pp. 9104 – 9105, as well as Figures 3 and 4), thereby meeting the limitations of claim 67. Rats were used, meeting the limitation of claim 68. BrdU was used as the marker of cell division, meeting the limitation of claim 70. The hippocampus was examined, meeting the limitations of claim 71 (see Figure 2). The animals were killed by transcardial perfusion (see paragraph spanning pp. 9104 – 9105), brain tissue was sectioned, labeled with anti-BrdU antibody, and cells were counted (see p. 9105, first column, under Immunohistochemistry), meeting the limitations of claim 72.

On p. 12 of the remarks, applicant argues that Malberg does not anticipate the claims because she does not teach administration of BrdU after administration of fluoextine. Applicant's arguments has been fully considered but are not found persuasive. While applicant is correct that in one series of experiments BrdU was administered before the antidepressant, in

other experiments the antidepressant was administered first. See particularly p. 9105, Figure 1, part A. This timeline indicates administration of antidepressants (ADT) for 1 – 28 d, then administration of BrdU, followed by sacrifice 2 hr – 28 days later. Furthermore, the sentence spanning pp. 9104 – 9105 clearly indicates that "rats were administered BrdU (4 x 75 mg/kg every 2 hr; Sigma, St. Louis, MO) 4 d after the last antidepressant or haloperidol treatment". Malberg explicitly teaches each and every element of claims 67, 68, and 70 – 72.

14. Claims 67, 68, 70 – 72 and 89 – 91 are rejected under 35 U.S.C. 102(b) as being anticipated by Lai et al. (Proceedings of the Second Joint EMBS/BMES Conference. October 23 – 26, 2002, p. 743 – 744), as evidenced by Frank-Kamenetsky et al. (reference 28 on the information disclosure statement filed 10 December 2004). The reasons why Lai is deemed to meet the limitations of the claims are set forth in the previous office action. Applicant argues, on p. 14 of the remarks, that Lai fails to anticipate the claims because Lai teaches only a single administration of the agent, whereas claim 67, from which all other rejected claims depends, requires administering the agent for several days to one month. The examiner disagrees. Lai 2002 teaches a single injection of an adenovirus comprising a nucleic acid which encodes a protein that upregulates the sonic hedgehog pathway. However, this single injection is sufficient to effect long-term administration of said protein. Lai 2002 teaches that the virus is active 14 days after administration (see p. 744, first column, final paragraph). The single injection of the virus resulted in long-term administration of the encoded protein, as evidenced by the finding that animals receiving the sonic hedgehog virus had 3.3-fold more BrdU-positive cells than those receiving a virus encoding green fluorescent protein when the BrdU was administered starting 14 days after the virus was administered. Claim 67 does not require multiple injections of the agent, merely that the agent is administered for several days to one month. Thus Lai 2002 fairly meets the limitation of claim 67 as well as dependent claims 68, 70 – 72 and 89 – 91.

15. Claims 67 – 68, 70 – 72, and 89 – 91 are rejected under 35 U.S.C. 102(a) as being anticipated by Lai 2003 (cited by applicant on the IDS filed 10 December 2004). The reasons why Lai 2003 is deemed to anticipate the claims is provided in detail in the previous office action. Applicant argues, on p. 15 of the remarks, that because Lai teaches only a single injection of the virus the reference fails to meet the limitation "administering ... for several days to one month" recited in claim 67. The examiner disagrees. Lai 2003 teaches a single injection of an adenovirus comprising a nucleic acid which encodes a protein that upregulates the sonic hedgehog pathway. However, this single injection is sufficient to effect long-term administration

of said protein. Lai 2003 teaches that the virus is active 14 days after administration (see p. 22, second column; both GFP and Shh are identified in the brains of animals injected with the respective viruses 2 weeks after injection). The single injection of the virus resulted in long-term administration of the encoded protein, as evidenced by the finding that animals receiving the sonic hedgehog virus had 3.3-fold more BrdU-positive cells than those receiving a virus encoding green fluorescent protein when the BrdU was administered starting 14 days after the virus was administered (see p. 23 first column). Claim 67 does not require multiple injections of the agent, merely that the agent is administered for several days to one month. Thus Lai 2002 fairly meets the limitation of claim 67 as well as dependent claims 68, 70 – 72 and 89 – 91.

Claim Rejections - 35 USC § 103

16. Claims 67 and 89 – 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frank-Kamenetsky (cited by applicant on IDS filed 10 December 2004) in view of Wallace (cited in previous office action).

The reasons why the agents taught by Frank-Kamenetsky are deemed to meet the structural and functional limitations recited in claims 89 – 92 are set forth in the previous office action. Briefly, Frank-Kamenetsky teaches the structures Hh-Ag 1.1, Hh-Ag 1.2, and Hh-Ag 1.3 recited in claim 92 and teaches that Hh-Ag 1.1 activates the Sonic hedgehog pathway *in vivo*, and that it is an antagonist of Patched and an agonist of Smoothened. Frank-Kamentsky et al. teach a method of determining whether said compound induces proliferation of neuronal precursor cells *in vitro* (see p. 10.3, In vitro assay of neuronal precursors). This assay included administration of the agonist to neuronal cell cultures, followed by administration of ^{3}H-thymidine two days later (see p. 10.17, paragraph spanning the two columns, which teaches the details of the method) and subsequent monitoring of incorporation. Frank-Kamentsky does not teach a method of determining whether an Hh-Ag 1.1 or any agonist of the sonic hedgehog pathway increases neurogenesis *in vivo*, but does explicitly contemplate the administration of Hh-Ag 1.1 as a therapeutic agent (see particularly p. 10.16, second column "Therapeutic potential of a Hh-pathway agonist"). Frank-Kamenetsky teaches each and every element of claim 67 with the exception that the method is *in vitro*, not *in vivo*.

Wallace teaches an in vivo assay to determine whether agents in the Sonic hedgehog (Shh) pathway change the amount of BrdU incorporated into brain tissue. Wallace's assay is a reasonable in vivo counterpart for Frank-Kamentsky's *in vitro* assay. Specifically, Wallace

teaches administration of anti-Shh antibodies to non-human animal subjects, followed by administration of BrdU (2 injections were given 2 hours apart), sacrifice of the animals 2 hours after the final BrdU injection (see p. 446, second column), quantitatively determining the incorporation of BrdU into the subject's brain tissue, and comparing the amount so determined to the amount determined to tissue from animals to which the agent was not administered (see sentence spanning pp. 446 – 447 and Figure 3). Wallace does not explicitly teach that the agent's ability to increase brain progenitor cell division is indicated by an increase in the amount of compound incorporated, but does implicitly teach this, as she teaches the converse: Wallace's intent in the experiment was "[t]o determine whether the treatment reduced proliferation in the EGL", the external granule layer, which is a brain region. One of ordinary skill in the art would clearly recognize that by teaching that a decrease in BrdU-positive cells is indicative of a decrease in proliferation, an increase in this marker would be indicative of an increase in brain progenitor cell division.

It would have been *prima facie* obvious to one of ordinary skill in the art to administer the agents of Frank-Kamentsky in the *in vivo* assay of Wallace, with a reasonable expectation of success. The motivation for doing so would be to determine if in fact Hh-Ag 1.1 was able to induce neurogenesis *in vivo*, as it had been shown capable of doing so *in vitro*, and Frank-Kamentsky et al. clearly contemplated the use of Hh-Ag 1.1 as a therapeutic agent in their test indicative of a use in neurodegenerative diseases. It would be reasonable to expect success, as Frank-Kamenetsky teaches the agent induces an increase in proliferation of neuronal precursors *in vitro*, and Wallace implicitly teaches that agents which increase incorporation of BrdU indicate an increase in proliferation *in vivo*. Furthermore, both Frank-Kamentsky and Wallace used nucleotides or nucleotide analogs as the compounds which are markers of cell division; Frank-Kamentsky used ^{3}H-thymidine whereas Wallace used BrdU, but both are incorporated into the DNA of dividing cells and are used interchangeably as markers of cell division.

Applicant argues, on p. 17 of the remarks, that Wallace fails to teach or suggest every element of claim 67 because she does not teach administration of agents which upregulate the Shh pathway, and that Frank-Kamenetsky fails to overcome the deficiencies of Wallace.

Applicant's arguments have been fully considered but are not deemed persuasive. The examiner acknowledges that Wallace does not teach administration of agents which upregulate the Shh pathway. However, Frank-Kamentsky clearly overcome the deficiencies of Wallace, as

they teach that Hh-Ag 1.1 is an agent which upregulates the Shh pathway (see p. 10.6, second column), that administration of Hh-Ag 1.1 induces brain-progenitor cell division *in vitro*, and contemplate its administration *in vivo*. Applicant also argues that Frank-Kamentsky does not teach administration of the compound which is a marker of cell division after administration of the agent and thus the examiner's conclusion of obviousness is not proper. Applicant's arguments have been fully considered but are not persuasive. Frank-Kamentsky does not teach *in vivo* administration of the marker of cell division after *in vivo* administration of the agent, however they do teach *in vitro* administration of the marker of cell division after the *in vitro* administration of the treatment agents (see p. 10.17, paragraph spanning the two columns). Furthermore Wallace teaches *in vivo* administration of the compound which is a marker of cell division after the administration of the agent. It would be obvious to one of ordinary skill in the art to administer the compound which is a marker of cell division after the administration of the agent, as both Wallace and Frank-Kamenetsky teach this. Furthermore it would be reasonable to expect success, as both Frank-Kamenestsky and Wallace teach that the amount of BrdU incorporated into cells is proportional to the amount of proliferation.

Conclusion

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
September 1, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
9-6-05